REMARKS

Claims 1-77 were pending in the application. Claims 1-33 and 44-77 have been withdrawn from further prosecution as drawn to non-elected groups. Claim 34 has been amended and new claim 78 has been added. Accordingly, upon entry of the present amendment, claims 1-78 will be pending in the instant application.

Support for the amendments to the claims may be found throughout the specification and claims, as originally filed. *No new matter has been added.*

Any amendments to and/or cancellation of the claims are not to be construed as an acquiescence to any of the rejections set forth in the instant Office Action, and were done solely to expedite prosecution of the application. Applicants hereby reserve the right to pursue the subject matter of the claims as originally filed in this or a separate application(s).

Election/Restriction

The Examiner has withdrawn claim 75 from further consideration. In particular, the Examiner is of the opinion that

> [c]laim 75 is drawn to a reach-through product claim and is distinct as capable of being made by other methods (such as chemical synthesis) and burdensome to search, since the search for products, which might include the well known drug Metformin, would be entirely different from the search for the method.

Applicants respectfully traverse the withdrawal of claim 75, and submit that this claim should be included in the originally elected invention (Group XV) which was elected in the Response to the Restriction Requirement dated November 21, 2003. It is respectfully submitted that a sufficient search and examination with respect to the claimed invention can be made without

without serious burden on the Examiner. Accordingly, Applicants respectfully request reconsideration of the withdrawal of claim 75.

Rejection of Claims 34-36 and 38-43 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 34-36 and 38-43 under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for the direct measurement of PGC-1 expression as in claim 37, does not reasonably provide enablement for the use of surrogates such as glucose output or expression of one of phosphoenolpyruvate carboxykinase, glucose-6-phosphate or fructose-1,6- bisphosphatase as in claims 38-41." Furthermore, the Examiner points to the Wands Factors, and is of the opinion that, with respect to the breadth of the claims, "[t]he claims encompass the use of any surrogate for analysis of PGC-1 including those specifically identified in claims 40 and 41." The Examiner also states that

> [t]he quantity of experimentation in this area is large since there is significant variability in the expression of PGC-1 depending upon the cell type, cell environment as discussed above regarding temperature, insulin treatment, chemotherapeutic or other treatments which is an inventive, unpredictable and difficult undertaking in itself, and efficacy of other elements as true surrogates for PGC-1 expression linked with gluconeogenesis would need to be demonstrated in a variety of different cell type models. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

With respect to the state of the prior art, the Examiner is of the opinion that

> [t]he art teaches that many factors may induce PGC-1 expression and that many factors which are responsive to PGC-1 may be induced by other signals. . . With regard to the use of secondary measurements to determine PGC-1 expression, it is entirely unpredictable whether, for example, a compound which modulates glucose output will perform this modulation a PGC-1 pathway had induce or repress PGC-1, or operate by a different pathway. . . Barthel expressly teaches that multiple different pathways may affect glucose output, not all of which include PGC-1. Consequently, measurement of glucose output may have no relevance for the PGC-1 expression status of cells induced with some compounds. . . Thus, compounds which interact with p300

> may affect glucose output without altering the level of PGC-1, for example. Barthel provides numerous other pathways which may affect glucose output without a direct effect on PGC-1 expression levels (see pages e686-e688). Further, with regard to the three specific genes listed, each of these genes is activated by proteins other than PGC-1. . . So in the case of the fructose 1,6-bisphosphatase gene, compounds which induce or repress NK-kB, SP1 or USF1/USF2 may directly impact the expression of the gene without any concomitant effect on the expression of PGC-1. Therefore, the prior art demonstrates that there are multiple pathways for the expression and activation of each of the cited reporter elements in claims 38-41 and that these reporter elements will not necessarily demonstrate expression of PGC-1, but rather will simply show some effect. It would require direct measurement of PGC-1 expression, as in claim 37, to demonstrate that the compound is, in fact, altering the expression or activity of PGC-1.

With respect to the guidance provided in Applicants' specification, the Examiner is of the opinion that

> [t]he specification, while suggesting the use of surrogate reporter systems, does not provide sufficient basis to verify whether these surrogates will function to show a change in the expression or activity of PGC-1. While the specification, for example, shows an association between glucose output and PGC-1 expression (see example 3 beginning on page 77), this showing that PGC-1 is capable of impacting glucose output does not show that PGC-1 expression is necessary essential for a change in glucose output. . . While sometimes, for some unpredictable set of compounds, PGC-1 will be induced, the specification provides no guidance on how to determine, based solely upon a measurement of glucose output, or expression of one of phosphoenolpyruvate carboxykinase, glucose-6-phosphate or fructose 1,6 bisphosphatase, whether PGC-1 was or was not modulated in expression or activity.

Applicants respectfully traverse the foregoing rejection. Applicants' respectfully submit that one of ordinary skill in the art would be able to make and use the claimed invention using only routine experimentation for at least the following reasons. Claim 34, as amended, is directed to a method for identifying a compound capable of modulating gluconeogenesis comprising contacting a cell with a compound, and ***assaying the ability of the compound to modulate the expression of a PGC-1 nucleic acid molecule or the activity of a PGC-1 polypeptide***, to thereby identify a compound that modulates gluconeogenesis. The present

invention is based on the surprising discovery that PGC-1 can stimulate glucose production by activation of key regulatory enzymes of the gluconeogenic pathway. Direct measurement of PCG-1 expression is not required in order to identify a compound which modulates gluconeogenesis. Applicants' specification, clearly teaches the relationship between PGC-1 and gluconeogenesis. For example, at page 8, lines 26-32, Applicants' specification states that

> it has been found that expression of PGC-1 induces expression of the key gluconeogenic genes phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase, and fructose-1,6-bisphosphatese, causing increased glucose production in cells. PGC-1 also interacts directly with the PEPCK promoter and with HNF-4α and FKHR, key gluconeogenic transcription factors. Moreover, it has been found that the induction of these gluconeogenic genes and the resulting increase in glucose production, is dose specific.

Furthermore, Applicants' specification not only provides working examples pertaining to the measurement of PGC-1 expression using Northern blotting (*see* Examples 1, 2, and 3), but also includes several working examples which illustrate the relationship between PGC-1 and gluconeogenic genes. For example, Example 3 of Applicants' specification states that "a dose-dependent activation of the hepatic gluconeogenic enzymes was achieved by titrating the amount of the PGC-1 expression in cells. Furthermore, the elevation of PGC-1 stimulated the expression of gluconeogenic genes in the physiological range of this coactivator," and further states that "[t]hese data directly demonstrate the ability of PGC-1, at physiological concentrations, to potentiate the hepatic glucose output via transcriptional regulation of the gluconeogenic enzymes." Example 4 further provides that PGC-1 is a regulator of PEPCK, a gene which is critical in gluconeogenesis.

In addition, Example 9 of Applicants' specification describes *in vivo* alteration of gluconeogenesis by PGC-1 and states that

> [t]he ectopic ***PGC-1 expression resulted in a dramatic and uniform elevation in mRNA for glucose-6-phosphatase***, reaching levels equivalent

> to those observed in fasting animals. There was also an increased expression of PEPCK mRNA, although one control rat also had elevated PEPCK mRNA. These data together show that ***modulation of PGC-1 levels in the physiological range promotes expression of gluconeogenic genes and changes in glucose homeostasis.***

Accordingly, Applicants' specification provides sufficient basis to verify that the measurement of surrogates will clearly be sufficient to show a change in the expression or activity of PGC-1.

Applicants further submit that based on the teachings and guidelines of the present invention as disclosed in the application, in combination with the knowledge of one of skill in the art at the time the application was filed, the procedures for assaying the ability of the compound to modulate the expression of a PGC-1 nucleic acid molecule or the activity of a PGC-1 polypeptide are routine to one skilled in the art. As stated in *Forman*, "[t]he test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance." *Ex parte Forman*, 230 USPQ 546, 547 (Bd. App. 1986). As also pointed out by the Federal Circuit in *Northern Telecom, Inc. v. Datapoint Corp.*, 15 USPQ 2d 1321 (1990), "[i]t is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." 15 USPQ 2d at 1329. See, also *In re Brana*, 34 USPQ 2d 1436 (Fed. Cir. 1995).

In conclusion, Applicants submit that the specification is enabling for the claimed method, *i.e.*, assaying the ability of the compound to modulate the expression of a PGC-1 nucleic acid molecule or the activity of a PGC-1 polypeptide, to thereby identify a compound which modulates gluconeogeneis. Reconsideration and withdrawal of the §112, first paragraph rejection is therefore requested.

Rejection of Claims 34-37 and 41-43 Under 35 U.S.C. §102

Claims 34-37 and 41-43 have been rejected under 35 U.S.C. §102. Specifically, claims 34-35 and 37 have been rejected under 35 U.S.C. §102(b) as being anticipated by Wu, *et al.* Claims 34-36 and 42-43 have been rejected under 35 U.S.C. §102(b) as being anticipated by Yu, *et al.*, and claims 34-37 and 41-43 have been rejected under 35 U.S.C. §102(e) as being anticipated by Spiegelman, *et al.*

The Examiner has rejected claims 34-35 and 37 under 35 U.S.C. §102(b) as being anticipated by Wu, *et al.* (*Cell* (1999) 98:115-124). In particular, the Examiner is of the opinion that

> Wu teaches a method comprising: a) contacting a cell with a compound (see page 117, figure 2, where myoblasts were treated with 100 nM T3); b) determining whether PGC-1 expression was modulated (see page 117, figure 2, panel A, where PGC-1 mRNA expression is shown). With regard to claim 35, Wu teaches that treatment with a compound induces PGC-1 activity (see page 117, columns 1 and 2). With regard to claim 37, Wu teaches measurement of PGC-1 by northern blotting (see page 117, figure 2)

The Examiner has rejected claims 34-36 and 42-43 under 35 U.S.C. §102(b) as being anticipated by Yu, *et al.* (*Am. J. Physiol. Endocrinol. Metab.* (Aug 2000) 279.-E433-446). In particular, the Examiner is of the opinion that

> Yu teaches a method comprising: a) contacting a hepatocyte cell with a compound, here LPS (see page e436, column 2, where mice were treated with LPS); b) determining whether PGC-1 expression was modulated (see page 437, figure 3, where PGC-1 mRNA is measured). With regard to claim 35, Yu teaches that treatment with a compound induces PGC-1 activity in skeletal muscle cells (see page e437, figure 3). With regard to claim 36, Yu teaches that treatment with a compound decreases PGC-1 activity in liver cells (see page e437, figure 3). With regard to claims 42-43, Yu teaches the use of hepatocytes from whole liver, which inherently comprises primary hepatocytes (see page e436, column 2).

The Examiner has rejected claims 34-37 and 41-43 under 35 U.S.C. §102(e) as being anticipated by Spiegelman, *et al.* (U.S. Patent 6,166,192). In particular, the Examiner is of the opinion that

> Spiegelman teaches a method (also see column 36, lines 47-67) comprising: a) contacting a hepatocyte (liver cell) with a compound, here insulin (see column15, lines 1-31); b) determining whether PGC-1 expression was modulated (see column 15, lines 1-10, where glucose output is used as a surrogate for PGC-1 expression). With regard to claims 35 and 36, Spiegelman teaches that treatment with a compound may increase or decrease PGC-1 activity (see column 15, lines 8-10). With regard to claim 37, Speigelman teaches the use of northern blotting (see column 40, line 53). With regard to claim 41, Spiegelman expressly teaches measurement of glucose output (see column 15, lines 1-10). With regard to claims 42-43, Spiegelman teaches the use of liver cells, which inherently comprises primary hepatocytes (see column 15, lines 1-10).

Applicants respectfully traverse the foregoing rejections under 35 U.S.C. §102 and request reconsideration. As the Examiner is well aware, for a prior art reference to anticipate a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987). Claim 34, as amended, and dependent claims 35-37 and 41-43 are directed to ***a method for identifying a compound capable of modulating gluconeogenesis*** comprising contacting a cell which expresses PGC-1 with a compound, and assaying the ability of the compound to modulate the expression of a PGC-1 nucleic acid molecule or the activity of a PGC-1 polypeptide, thereby identifying a compound capable of modulating gluconeogenesis.

Wu, *et al.* teach the role of PGC-1 in regulating ***adaptive thermogenesis in skeletal muscle***. Specifically, Wu, *et al.* teach that PGC-1 increases total respiration capacity and mitochondrial uncoupling in a cell type-selective manner, stimulates mitochondrial biogenesis through the induction of UCP-2, NRF-1 and NRF-2 gene expression, coactivates NRF-1 on the

promoter of mtTFA which is a direct regulator of mitochondrial replication/transcription (See entire document).

Yu, *et al.* disclose an analysis of ***thermoregulatory control*** in mice administered LPS to induce acute hypothermia. In particular, Yu, *et al.* teach that there are large changes in UCP homolog mRNA abundance and PGC-1 expression as well as large metabolic shifts, *e.g.*, body temperature and metabolic rate shifts, that do not correlate with mitochondrial proton leak (See, for example, page E434, right column, first paragraph).

Spiegelman, *et al.* disclose the identification of novel PGC-1 nucleic acid and protein molecules. Spiegelman, *et al.* teach that PGC-1 is expressed in brown adipose tissue, skeletal muscle, heart, kidney, and brain, and acts in combination with PPARγ, a nuclear hormone receptor which regulates many fat-specific genes and ***adipogenesis***. Furthermore, these documents teach that the UCP promoter region contains a PPARγ response element, suggesting that PPARγ also modulates ***thermogenesis*** by participating in oxidative metabolism (See, for example, column 8, line 64 through column 9, line 1).

In contrast, the instant specification teaches that PGC-1 is a major regulator of ***gluconeogenesis***, and the pending claims are directed to screening methods for identifying compounds which modulate ***gluconeogenesis*** utilizing PGC-1. The claims are not directed to the chemical structure of PGC-1, *per se*. Yu, *et al.*, Wu, *et al*, and Spiegelman, *et al.* do not provide any teaching or suggestion whatsoever that PGC-1 is involved in any way in the modulation of gluconeogenesis. Furthermore, Applicants respectfully submit that Yu, *et al.*, Wu, *et al*, and Spiegelman, *et al.* ***do not teach or suggest methods for identifying compounds which are capable of modulating gluconeogenesis*** as is claimed in the instant application.

Therefore, for the reasons set forth above, Yu, *et al.*, Wu, *et al*, and Spiegelman, *et al.* either alone or in combination, do not teach or suggest each and every limitation of the claimed

invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing rejections.

Rejection of Claims 34-37 and 41-43 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 34-37 and 42-43 as being unpatentable over Yu, *et al.* in view of Wu, *et al.* Specifically, the Examiner states that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to *(sic)* since northern blotting is a known equivalent technique for measurement of mRNA levels as shown by Wu".

Applicants respectfully traverse this rejection. To establish a *prima facie* case of obviousness, it is necessary for the Examiner to present evidence, preferably in the form of some teaching, suggestion, incentive or inference in the applied references, or in the form of generally available knowledge, that one having ordinary skill in the art would have been motivated to make the claimed invention and would have had a reasonable expectation of success in making the claimed invention. Under section 103, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure" (*Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.* 927 F.2d 1200, 1207, 18 USPQ2d 1016 (Fed. Cir. 1991), quoting *In re Dow Chemical Co.,* 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed Cir. 1988)). Moreover, when a combination of references are used to establish a *prima facie* case of obviousness, the Examiner must present evidence that one having ordinary skill in the art would have been motivated to combine the teachings in the applied references in the proposed manner to arrive at the claimed invention. See, *e.g., Carella v. Starlight Archery*, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986); and *Ashland Oil, Inc. v. Delta Resins and Refractories, Inc.*, 776 F.2d 281, 227

USPQ 657 (Fed. Cir. 1985). ***Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations*** (M.P.E.P. 2143).

Wu, *et al.* and Yu *et al.* fail to teach each and every limitation of the claimed invention. As stated above, Wu, *et al.* describe the role of PGC-1 in regulating ***adaptive thermogenesis***. Yu, *et al.* provide results of an analysis of UCP and PGC-1 in ***thermoregulatory control***.

Claim 34 is directed to ***a method for identifying a compound capable of modulating gluconeogenesis*** comprising contacting a cell which expresses PGC-1 with a compound, assaying the ability of the compound to modulate the expression of a PGC-1 nucleic acid molecule or the activity of a PGC-1 polypeptide, and identifying a compound which modulates the expression of a PGC-1 nucleic acid molecule or the activity of a PGC-1 polypeptide, ***thereby identifying a compound capable of modulating gluconeogenesis***.

Wu *et al.* and Yu *et al.* alone or in combination, fail to teach or suggest use of PGC to identify compounds capable of modulating gluconeogenesis. Therefore, Applicants respectfully request reconsideration and withdrawal of the foregoing rejection of claims 34-35 and 37 under 35 U.S.C. §103(a).

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call the undersigned at (617) 227-7400.

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Respectfully submitted,

By _____

DeAnn F. Smith, Esq.
Registration No.: 36,683
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney for Applicants